REMARKS/ARGUMENTS

1. Amendments

Claims 1, 4, 6, 9-14, 16-34, and 40-49 are in the application. Claims 45-49 have been withdrawn.

Claim 1 has been amended to recite that the third polypeptide is an IgE class immunoglobulin. Support for this amendment can be found in claim 5. Claim 5 has been canceled. Claims 12 and 13 have been amended to clarify that the IgE class immunoglobulin of claim 1 binds to the receptor. Claim 14 has also been amended. These amendments are made without prejudice to filing divisional or continuation applications directed to the canceled subject matter.

2. Rejection under 35 U.S.C. § 112, first paragraph. (Enablement)

Claims 1, 4-5, 9-14, 16-34 and 40-44 stand rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for (1) isolated fusion molecule comprising hinge CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO:2 encoded by SEQ ID NO:1 capable of binding to a native IgG inhibitory receptor directly fused to a full length myelin basic protein comprising SEQ ID NO:12 or a peptide from myelin basic protein epitope consisting of the amino acid sequence of SEQ ID NO:13, wherein the fusion molecule is capable of specific binding to a native IgE receptor through a myelin protein specific IgE antibody, (2) the said fusion protein wherein the native IgG inhibitory receptor is a low-affinity FcγRIIb IgG receptor, (3) the said fusion protein wherein said IgE receptor is a high-affinity FcϵRI IgE receptor or a low affinity FcϵRII IgE receptor. The specification allegedly does not reasonably provide enablement for any fusion molecule as set forth in claims 1, 4-5, 9-14, 16-34 and 40-44 for treatment or "prevention" of any autoimmune disease.

Claim 1 recites an isolated fusion molecule comprising a first polypeptide sequence comprising at least 85% identity with an IgG heavy chain constant region sequence capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at

least 90% sequence identity to at least a portion of the amino acid sequence of basic myelin protein (MBP) and capable of specific binding to an IgE class immunoglobulin

Applicant traverses the rejection for the following reasons.

The test for enablement entails an analysis of whether one skilled in the art is able to practice the invention using information disclosed in the application and information known in the art without undue or unreasonable experimentation (MPEP § 2164.01; see In *re Wands,* 858 F.2d 731, 8 USPQ 2d 1400, [Fed. Cir. 1988]). A finding of lack of enablement and determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re Wands* factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of ordinary skill in the art; 3) guidance provided in the specification, and 4) the state of the prior art. "[H]ow a teaching is set forth, by specific example or broad terminology, is not important"; and furthermore still, "[l]imitations and examples in the specification do not generally limit what is covered by the claims" (MPEP § 2164.08). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* 448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 197 1), cert. denied, 404 U.S. 10 18, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972).

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

Proper application of the legal standard must lead to the conclusion that all claims pending in this application are fully enabled.

The nature of the invention

The present invention concerns certain novel fusion molecules that are capable of cross-linking a native IgG inhibitory receptor with a native IgE receptor. The fusion molecules comprise a sequence comprising at least 85% identity to IgG heavy chain sequence linked to a polypeptide autoantigen sequence which comprises at least 90% identity to at least a portion of myelin basic protein and is capable of specifically binding to an IgE class immunoglobulin. The purpose of these molecules is to allow the myelin basic peptide to function as an immunogen while any fusion peptides that reacted with IgE loaded mast cells would not trigger an adverse reaction.

While the therapeutic strategy and the construct underlying the present invention is both novel and unobvious, the fusion molecules themselves have a relatively simple structure, and can be made and tested by standard techniques that were well known in the art at the time of making the present invention. Furthermore, at the time the present invention was made, there was a lot of information known in the art about the interaction of IgG inhibitory receptors and IgE receptors with antibody constant regions, which provides valuable information for the construction of the fusion molecules of the present invention. Accordingly, although unpredictability in the field of recombinant DNA technology is generally viewed as relatively high, the unpredictability in the particular field to which the present invention pertains is of lesser degree. Example 2 of the specification provides the method for generating the fusion molecules.

It is well established that the level of skill in the art of recombinant DNA technology is relatively high, and is typically represented by the knowledge of a Ph.D. scientist with several years of experience in the pertinent field.

The Office Action indicates that there is insufficient guidance as to the structure and length of the first polypeptide. The specification allegedly does not teach which amino acids within the full-length sequence of all IgG heavy chain constant region are critical and can or cannot be changed such as substitution etc and whether the resulting IgG heavy chain constant region merely having 85% sequence identity with an IgG heavy chain constant region still binds to which native IgG inhibitory receptor.

Applicants maintain that the specification provides adequate disclosure for the following reasons. Applicant points out that Claim 1 and all claims dependent on Claim 1 contain the functional limitation that the IgG domain has the ability to bind to the native IgG inhibitory receptor. The sequence of the IgG heavy chain domain was known in the art at the time of filing. Figure 1 provides the nucleotide sequence encoding the human IgG1 heavy chain constant region. Figure 2 provides the amino acid sequence. Page 26 of the specification provides numerous references which describe the sequences of immunoglobulin heavy chain constant regions, such as Ellison et al., Nucleic Acid Res. 10:4071-79 (1982). The Specification teaches which amino acids are necessary for IgG receptor binding (see page 35, lines 1 - 25) as well as methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 55, lines 15-25). Thus, use of the term "comprising" does not result in an infinite number of fusion molecules with unpredictable activities as the Examiner contends, rather identification of fusion molecules that meet the limitation of the claims would be routine and would not require undue experimentation.

Furthermore, it is not necessary to provide the amino acid sequence in the specification where the sequence is known in the art. The United States Court of Appeal for the Federal Circuit held in *Capon v. Eshar* (418 F.3d 1349: 2005 (U.S. App); 76 USPQ (BNA) 1078) that:

> *[t]he chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specification do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.*

The Office action states that the term "comprising" expands the IgG heavy chain constant region to include the Fab region of the whole IgG. Without knowing the length of the first polypeptide, it is allegedly not clear how one of ordinary skill in the art could determine the sequence identity that is based on the total number of amino acids in the first polypeptide. The Office Action states that with regard to the percentage sequence identity (claims 1 and 18-21), in addition to the lack of sequence for the first polypeptides in the fusion molecule mentioned above, there is insufficient guidance as

to which amino acids within the full-length IgG constant region can be modified and yet maintain its function.

Applicant notes that the term "IgG heavy chain constant region" is defined in the specification at pages 26 and 36. It does not include the Fab region. Accordingly the term "comprising 85% of the IgG heavy chain constant region" means that the first polypeptide must exhibit at least 85% identity with the IgG heavy chain constant region. There may of course be additional amino acid residues included in the fusion peptide. However, one of ordinary skill in the art would know whether the fusion molecule contained an amino acid sequence with 85% identity to the IgG heavy chain constant region. Applicant points out that the Specification describes methods for the determination of percent identity between two amino acid sequences (see Specification, page 23, lines 4 - 13). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Also, one of ordinary skill in the art will recognize that the prior art provides numerous sources that describe IgG Fc sequences highly homologous to the Fc sequences of SEQ ID NO: 3 *(see,* the Specification at page 26, line 19 - page 27, line 6). Furthermore, Applicant asserts that one of ordinary skill in the art has a sufficiently high level of technical competence to experimentally identify novel Fc sequences having at least 85% sequence identity with the constant domain sequences of SEQ ID NO: 3 using the NCBI BLAST sequence identity values or the hybridization methods provided in the Specification (see, page 23, line 16 to page 24, line 12). Alternatively, one of ordinary skill in the art can readily engineer novel Fc domains exhibiting at least 85% sequence identity with the constant domain sequences of SEQ ID NO: 3 using recombinant DNA/protein engineering techniques. Thus, detailed protocols for the construction of fusion molecules having at least 85% sequence identity with a known Ig constant domain in the Specification is not necessary in order for one of ordinary skill to practice the claimed invention without undue experimentation.

The Examiner cites Stryer et al., that a protein is highly dependent on the over all structure of the protein itself. The Examiner cites Ngo et al., that amino acid positions within the protein that can tolerate change such as conservative substitutions which are critical to maintain the protein's structure/function will require guidance. The Examiner

cites Tao et al., as teaching that the ability to activate complement and to bind to FcγRI both of which are dependent on the CH2 domain of IgG heavy chain. Tao allegedly teach that a specific amino acid substitution in the CH2 domain of human IgGs affected the structure and functional properties of the human IgGs.

Applicants maintain that it is well-known in the art that many, if not most, polypeptides of the invention exhibiting at least 85% sequence identity with the constant domain sequence of SEQ ID NO: 3 will retain biological activity. This is because one of ordinary skill in the art is fully aware of amino acid substitutions that are either less likely or not likely to significantly affect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid). For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in J. U. Bowie, *et al.*, "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-10 (1990) (previously provided), wherein the authors indicate that proteins are surprisingly tolerant of amino acid substitutions.

In addition, amino acids in the fusion proteins of the present invention that are essential for function can be easily identified by methods well-known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (*see*, *e.g.*, Cunningham and Wells, *Science* 244:1081-85 (1989) (previously provided)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity, for example, as taught in the routine assays provided in the specification.

The claims currently recite peptide sequences associated with biological activity. This biological activity with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, is believed to sufficiently define the claimed genus such that, one of ordinary skill in the art, at the effective date of the present application, would have known how to make and use the claimed peptide sequences without undue experimentation. As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation," *In re Certain Limited-charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*

Massachusetts Institute of Technology v A.B. Fortia 774 F 2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *M.P.E.P. 2164.01*

The Office Action states that there is insufficient guidance as to the structure and length of the second polypeptide autoantigen within the fusion protein without the amino acid sequence. There is allegedly insufficient guidance was to which "portion" of the MBP in the second polypeptide autoantigen is part of the fusion molecule.

In response, Applicant maintains that one of skill in the art would know which portion was required for binding to IgE class immunoglobulin. The sequence for MBP was known in the art prior to the date of Applicant's filing. Applicant provides a number of references in the specification at page 46 which provide the sequence for MBP, see for example Warren et al., Proc. Natl. Acad. Sci USA 92:11061-11065 (1995). The specification identifies the MBP epitope necessary for binding with the autoantibody as MBP83-99. Furthermore, the Examiner references Warren et al., (1995 abstract) as teaching that the administration of MBP75-95 resulted in significant autoantibodies, but the administration of MBP35-58 did not affect the anti-MBP level. The specification at Example 2, pages 80 – 82 provides a method for identifying and generating the MBP DNA sequences.

One of ordinary skill in the art, based on the disclosure in the specification could construct MBP amino acid sequences having at least 90% sequence identity with the known MBP protein. The examples provides a method for generating the fusion molecule and methods for testing the fusion molecule for its ability to prevent basophile release and also methods to test for its abiLity to suppress anaphylaxis. Accordingly, one of ordinary skill in the art would certainly know which portion of the MBP protein is specifically bound by autoantibodies, how to generate a fusion molecule with that portion and how to test the resulting fusion molecule for the ability of the MBP portion to bind to IgE antibodies.

The Office Action cites McDevitt et al., as allegedly teaching that administering autoantigen comprising a "portion" of an autoantigen to mice resulted in the prompt onset of an immediate hypersensitivity and death of animal. Without guidance as to the portion or epitope of autoantigen to be fused, it is allegedly unpredictable which fusion mocleucule is effective for treating autoimmune disease.

The invention is directed to a fusion protein comprising the portion of the autoantigen which results in an allergic reaction fused to the heavy chain constant region. The fusion of the autoantigen to the heavy chain results in suppression of the allergic reaction. Accordingly, based on the discussion regarding the MBP portion, one skilled in the art would understand what portion of the MBP to use.

The Office action indicates that it is known that the relationship between the amino acid sequence of a protein and its tertiary structure are not well understood and are not predictable, again citing Ngo et al., The Office Action states that even a single amino acid change or different in a proteins amino acid sequence can have dramatic effects on the protein's function., citing Mikayama et al.

Applicants note that as discussed above, the sequence for the constant region of IgG was well known. The sequence for the MBP was well known, as evidenced by the specification. Thus one skilled in the art would know which amino acids could be changed and still retain function. Furthermore, claim 1 contains functional language which requires that the IgG region be capable of specific binding to a native IgG inhibitory receptor and that the MBP portion be capable of specific binding to a igE class immunoglobulin. One skilled in the art could readily test any fusion molecule constructed to determine whether it had these functions.

The Examiner states that the term "percent" is relative and can be defined by the algorithm and parameter values set. The Examiner states that applicants have not disclosed the specific condition used to score sequence identity.

Applicants disagree. Page 23 of the specification provides the computer program software which may be used to score identity.

The Examiner cites Warrant et al. as allegedly teaching the administration of myelin basic protein fragment 35-58 to multiple sclerosis patients had no effect on the anti-MBP level, whereas administration of MBP 75-95 resulted in significant autoantibodies. Allegedly the specification does not teach which portion to administer.

In fact, the specification teaches that the portion to be administered is that portion which is specifically recognized by IgE antibodies specific for MBP so that the IgE antibodies will bind to the IgE receptor.

The Examiner states that Attwood et al. teach that protein function is contact dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable.

This rejection is misplaced for this application. This application is not directed to identifying a function of a protein based on sequence similarity. The sequences used in this fusion protein as well characterized sequences with known functions. The IgG sequence is well known. As the Examiner knows based on the references cited in the office action, the MBP sequence is well known. Withdrawal of this portion of the rejection is requested.

The Examiner states that the term "comprises " is open ended. It extends the hinge, CH2 and CH3 domains of a native human IgG sequence to include additional amino acids at either ends of the first polypeptide within the claimed fusion molecule, to include the light chain such as the Fab fragment.

Applicant must respectfully disagree. First applicants note that the compound is a fusion protein. In a full length antibody, the light chain is a separate polypeptide. Second, the present application describes, by way of example, additional non-essential but advantageous amino acid sequences and other elements that find use with the first and second polypeptides of the fusion molecules of the invention. For example, the first and second polypeptide sequences of the fusion molecule can be joined using various linkers (such as those described in the Specification at page 56, lines 4-16). Also, the fusion molecules may contain posttranslational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation and prenylation (see Specification page 21, lines 4 - 24). The Specification teaches that fusion polypeptide variants can be constructed that contain advantageous insertions of various amino acid sequences (page 21, line 25 to page 23, line 3), resulting in fusion molecules that have improved affinity for their respective IgG or IgE Fc receptors (Specification, page 34, line 24 to page 35, line 25). The fusion molecules of the invention can also comprise multiple copies of the IgG and autoantigens, as described in page 54, lines 18-21. Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 63, lines 20-22), and peptide sequence tags to facilitate

fusion molecule purification (page 63, line 32 to page 64, line 3) also find use with the fusion molecules of the invention.

As outlined above, the Specification provides sufficient guidance to make a variety of advantageous fusion molecules comprising first and second polypeptide sequences. Applicant submits that fusion molecules comprising first and second polypeptides are fully enabled in view of 1) guidance provided throughout the Specification[1] (as described above), 2) the routine nature of recombinant DNA engineering and the production of chimeric or variant polypeptides, as known in the art, and 3) the high level of technical competence of one of ordinary skill in the immunological, genetics and protein-chemistry arts. The routine nature of manipulation of DNA and protein molecules is well known, as evidenced by the publications cited in the Specification *(see,* especially, page 20, line 29 to page 21, line 24; page 64, lines 17 - 26). Detailed protocols for the construction of the fusion molecule variants described in the Specification is not necessary for one of ordinary skill to practice the claimed invention without undue experimentation.

The Office Action states that the first polypeptide sequence "comprises amino acids" encoded by any nucleic acid hybridizing under stringent conditions to which "portion" of the complement of the IgG heavy chain constant region nucleotide of SEQ ID NO:1 (claim 25) the nucleic acid that hybridizes to the complement of SEQ ID NO:1 could be an oligonucleotide which does not encode the whole IgG heavy chain constant region, let alone binding to a native IgG inhibitory receptor. Again the Office Action states that there is insufficient guidance as to the structure of the oligonucleotide that encodes which portion of the complement of IgG heavy chain.

Applicant assumes that this rejection is directed specifically at claim 25. Applicant respectfully disagrees. Applicant points out that Claim 1 and all claims dependent on Claim 1, including claim 25, contain the functional limitation that the IgG domain has the ability to bind to the native IgG inhibitory receptor and that the myelin basic protein (MBP) is capable of specific binding to an IgE class immunoglobulin. The

---

[1] Applicant points out that the guidance provided in the Specification is found both in the Experimental Example as well as in the description of other preferred embodiments elsewhere in the Specification.

Specification teaches which amino acids are necessary for IgG receptor binding (see *e.g.* page 35, lines 1 - 25) as well as methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 55, lines 15-25). The specification defines the term "portion" on page 29, lines 21 - 30. The specification teaches which amino acids comprise the epitopes of MBP (page 29, lines 7 to 11 and page 46, Table 2) Thus, use of the term "portion" does not result in an infinite number of fusion molecules with unpredictable activities as the Examiner contends, and the identification of fusion molecules that meet the limitation of the claims is routine and does not require undue experimentation.

The Office Action indicates that there is insufficient guidance as to the stringent hybridization conditions. The Examiner is directed to page 23 of the specification which recites the conditions for stringent hybridization. One skilled in the art would know how to determine whether the sequence hybridized under stringent conditions.

The Office Action also cites Skolnick et al., that sequence based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function.

The citation of this reference is misplaced here. Applicant is not identifying a function associated with a protein based on sequence homology of the protein to known peptides. Applicant has described a chimeric protein comprising two known sequences with known function. Accordingly, withdrawal of this portion of the rejection is respectfully requested.

The Examiner indicates that there is a lack of *in vivo* working examples demonstrating that the fusion molecule is effective for treating multiple sclerosis. The Examiner relies on Blanas et al., Couzin et al. and Mackay et al[2]. The Examiner states that the fusion molecule may be inactivated before producing an effect; the fusion molecule may not reach its targeted area.

---

[2] Applicant presumes that the Examiner intended to cite Davidson et al., (2001) New England J. of Med. 345(5) 340-350, Eds. MacKay & Rosen rather than MacKay et al. Although a request for clarification was raised in the previous response, the Examiner continues to refer to MacKay and has not clarified which reference is being cited. Applicant assumes that the Examiner means Davidson.

The legal standard with respect to in vitro or animal model data providing pharmacological activity was set forth by the United States Court of Appeals for the Federal Circuit in its opinion Cross v Iizuka 753 F. 2d 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985).

> *"We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vitro utility."*

Furthermore, M.P.E.P. 2107.03 (III) states that,

> *"[i]f reasonably correlated to the particular therapeutic or pharmacological utility, data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."*

Thus, the legal standard requires that *in vitro* or animal model data is acceptable as a basis for enablement.

Blanas indicates that oral administration of ovalbumin autoantigen in mice was found to induce a cytotoxic T lymphocyte response that could lead to the onset of autoimmune diabetes. Blanas does not discuss the MBP peptide or multiple sclerosis. Applicant's construct comprises the heavy chain constant region of the IgG fused to the MBP peptide. The fusion molecule acts to inhibit the autoallergic reaction. Blanas does not discuss the administration of a fusion molecule, let alone a fusion molecule comprising an autoantigen fused to the IgG heavy chain constant region, as claimed. Accordingly, the findings of Blanas cannot be applied properly to the currently claimed invention.

Couzin et al. (2003) is an article reviewing various clinical tests for the treatment and prevention of type I diabetes. Couzin does not discuss the MBP peptide, use of a fusion polypeptide or multiple sclerosis. For the reasons set forth for Blanas, the findings of Couzin et al. cannot be applied properly to the currently claimed invention. Furthermore, the legal standard sufficient to establish enablement of a compound is *in vitro* or *in vivo* animal model tests. In any case, human clinical trials are not required.

Davidson et al., states that two recent phase I clinical trials for treatment of multiple sclerosis by administering altered peptide ligands derived from MBP resulted in either hypersensitivity reactions or exacerbations of multiple sclerosis. (page 346) First, Davidson does not indicate that the altered peptide ligands derived from MBP are functionally attached to the IgG heavy chain constant regions. The purpose of the IgG Fc regions is to prevent the hypersensitivity reaction seen with the peptides as taught by MacKay. Accordingly, Davidson does not teach that the claimed invention will not work. Furthermore, the legal standard sufficient to establish enablement of a compound is *in vitro* or *in vivo* animal model tests. In any case, human clinical trials are not required.

McDevitt, allegedly indicates that administration of GAD autoantigen epitopes in NOD mice was found to induce immediate hypersensitivity that could lead to death. Applicant's fusion molecules comprise the heavy chain constant region of the IgG fused to the MBP peptide. The fusion molecule acts to inhibit the autoallergic reaction. McDevitt does not discuss the administration of a fusion molecule, let alone a fusion molecule comprising an autoantigen fused to the IgG heavy chain constant region, as claimed. Accordingly, the findings of McDevitt cannot be applied to the currently claimed invention. Indeed, use of an autoantigen fused to the IgG heavy chain constant region as proposed by Applicant would be the way to resolve the problem discussed by McDevitt.

Applicant previously enclosed later published papers which show that fusion molecules comprising an IgG constant region linked to an IgE constant region successfully reduces histamine release in animals. Clearly such compounds are not inactivated as suggested by the Examiner. Clearly these types of fusion molecules can be successfully administered to animals[3].

Furthermore, the appearance of IgG or other antibodies against the MBP portion of the fusion molecule would not be a problem because the purpose of the molecule is

---

[3] Zhu et al., "A novel human immunoglobulin Fcγ-Fcε bifunctional fusion protein inhibits Fcε RI mediated degranulation". (2002) *Nature Medicine* vol. 8 (5) 518-521; Kepley et al. "FcεRI-FcγRII coaggregation inhibits IL-16 production from human langerhans-like dendritic cells" (2003) *clinical Immunology* vo. 108 p. 89-94

to present the MBP as an "immunogen" while any reacted IgE loaded mast cells would be suppressed by the IgG Fc portion.

For the above reasons, Applicant asserts that the presently claimed invention is fully enabled under 35 U.S.C. § 112, first paragraph and respectfully requests that the Examiner withdraw this rejection.

3. Rejection under 35 U.S.C. § 112, first paragraph. (Written Description)

Claims 1, 4-6, 9-14, 16--34 and 40-44 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking written description. Specifically, the Examiner alleges that there is insufficient written description in the Specification for the same fusion molecules that were rejected on the basis of lack of enablement (see above, and Office Action, pages 7-8).

Claim 1 recites an isolated fusion molecule comprising a first polypeptide sequence comprising at least 85% identity with an IgG heavy chain constant region sequence capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of basic myelin protein (MBP) and capable of specific binding to an IgE class immunoglobulin.

Applicant traverses the rejection for the following reasons.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one of ordinary skill in the art can reasonably conclude that the inventor had possession of the claimed invention (e.g., *Vas-Cath, Inc. v. Mahurkar,* 935 F.2d at 563, 19 USPQ 2d at 1116 and *Gentry Gallery, Inc. v. Berkline Corp.,* 134 F.3d 1473, 45 USPQ 2d 1498 [Fed. Cir. 1998]). Applicant asserts that they have met this requirement. Applicant emphasizes that sufficient written description must be ascertained in view of one skilled in the art. "It is not required that the application describe the claim limitations in greater detail than the invention warrants. The description must be sufficiently clear that persons of skill in the art will recognize that the applicant made the invention having those limitations" *(Martin v. Mayer,* 823 F.2d 500, 3 USPQ 2d 1333 [Fed. Cir. 1987]).

Furthermore, it is not necessary to provide the amino acid sequence in the specification where the sequence is known in the art. The United States Court of Appeal for the Federal Circuit held in *Capon v. Eshar* that:

> *The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specification do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.*

The Examiner alleges that the Specification only discloses an isolated fusion molecule comprising a first polypeptide wherein the first polypeptide consists of a hinge-CH2-CH3 of human IgG1 constant region of SEQ ID NO:2 encoded by SEQ ID NO:1 fused to a full length myelin basic protein comprising SEQ ID NO:12 or a myelin basic protein epitope consisting of the amino acid sequence of SEQ ID NO:13 and (2) an isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO:1 fused to a human IgE constant region CH2-CH3-CH4 domains of SEQ ID NO:7 for inhibiting IgE mediated release of histamine. The Office Action states that with the exception of the specific fusion molecule mentioned above, there is insufficient written description about the structure associated with function of any and all fusion molecules mentioned above without the amino acid sequence.

Applicants must respectfully disagree. First Applicants note that part (2) of this statement is not the claimed invention, since the invention does not comprise IgE attached to IgG. Withdrawal of this part of the rejection is requested.

Second, as described above, the Specification describes multiple fusion molecules. For example, the Specification describes the construction of chimeric fusion molecules, see Example 2, pages 180-183. The Specification also describes fusion molecules where the first and second polypeptide sequences of the fusion molecule are connected by use of linkers (see Specification page 27, lines 4-15). Also, the fusion molecules may contain post translational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation or prenylation (as described in the Specification at page 21, line 4 - 24). The Specification describes advantageous fusion molecule variants (page 21, line line 25 - page 23, line 3), where the variants have

improved affinity for their respective IgG or IgE receptors (Specification, page 34, line 24 - page 35, line 25). The Specification describes fusion molecules comprising multiple copies of IgG and autoantigen (page 54, lines 18-21). Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 63, lines 20-22), and peptide sequence tags to facilitate fusion molecule purification the fusion molecules (page 63, line 32 to page 64, line 3) are also described.

In view of the fusion molecules described above and the level of skill in the art, Applicant asserts that sufficient representative fusion molecules are adequately described in the Specification (without undue detail) to support a genus of fusion molecules, as recited in Claim 1, and all claims dependent on Claim 1. Applicant respectfully requests withdrawal of this rejection.

The Examiner alleges that the Specification fails to provide sufficient written description of polypeptides having at least 85% sequence identity with the IgG constant domain sequences *(e.g.,* 85% sequence identity with SEQ ID NO: 3) where the molecules retain biological activity.

Applicant respectfully traverses the rejection. Applicant points out that the Specification describes methods for the determination of percent identity between two amino acid sequences (see Specification, page 23, lines 4 - 13). Also, the Specification provides examples of prior art that describes numerous Ig Fc polypeptides having at least 85% sequence identity with the Fc sequences of SEQ ID NO: 3 *(see,* the Specification at page 26, line 19 to page 27, line 6). The Specification also describes methods for the identification of Ig Fc sequences having at least 85% sequence identity with the constant domain sequences of SEQ ID NO: 3 (see the Specification at page 23, line 16 to page 24, line 12). Alternatively still, one of ordinary skill in the art can readily engineer novel Fc domains having at least 85% sequence identity with the constant domain sequences of SEQ ID NO: 3 using recombinant DNA/protein engineering techniques.

With respect to the second polypeptide, the sequence for MBP was known in the art prior to Applicant's filing. Applicant provides a number of references in the specification at page 46 which provide the sequence for MBP, see for example, Warren et al., Proc. Natl. Acad. Sci. USA 92:11061-65 (1995). The specification identifies the

MBP epitope necessary for binding with the autoantibody as MBP83-99. Clearly Applicant had possession of the invention at the time of filing.

Applicant points out that all pending claims reciting polypeptides having at least 85% sequence identity with IgG Fc domains *(e.g.,* having 85% sequence identity with SEQ ID NO: 3) contain the functional limitation that the polypeptides also have the ability to bind to the IgG cell surface receptor. The Specification provides a description of which amino acids are necessary for receptor binding and biological activity (page 35, lines 1-25) and methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 55, lines 15 - 25) are described.

Applicant argues that the Specification provides adequate written description for fusion molecules of claim 1, especially in view of the state of the prior art, and the high level of skill in the art.

The Office Action states that with regards to claim 9 there is allegedly inadequate written description about the "portion" of MBP without the amino acid sequence. Further the term "comprises" is open ended and allegedly expands the undisclosed "portion" to include additional amino acids at either or both ends.

Applicant disagrees that there is a lack of written description for claim 9. For the reasons set forth above, there is sufficient support for the portion of MBP which binds to IgE. Additionally, there is support for additional sequences which might be added to the fusion molecule.

The Office Action states that with regard to claim 10, the autoantigen sequence comprises the amino acid sequence of SEQ ID NO:13. The term comprises expands the sequence to include additional amino acids at either or both ends. There is allegedly insufficient disclosure about which amino acids to be added.

Applicant disagrees that there is a lack of written description for this claim. Applicant notes that claim 10 depends from claim 9 which depends from claim 1. Accordingly, the autoantigen sequence must be capable of specific binding to an IgE class immunoglobulin. For the reasons set forth above, there is support for additional sequences which might form part of the fusion molecule.

With regard to claims 18-21, the Office Action states that there is allegedly inadequate written description about which amino acids within SEQ ID NO: 3 of the first polypeptide could be changed.

Applicant disagrees for the reasons set forth above. In particular, SEQ ID NO:3 is known and regions for binding etc have been identified. Furthermore, the specification provides tests which can be conducted to ensure that the polypeptide is capable of binding an IgG inhibitory receptor. The invention has been adequately described.

The Examiner directs applicants attention to the Written Description guidelines. The Examiner is especially directed to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-111, Friday, January 5, 2001. Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office clearly states that the protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins is routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence. Accordingly, the claims are supported by the specification.

With regard to claims 22-24, the Office Action states that the term"comprises" expands the Ch2-Ch3 domains of a human IgG1 constant region to include the hinge, the Ch1 domain or the Fab fragment in the claimed protein. None of the fusion proteins in the specification as filed allegedly includes the CH1 domain or the Fab domain.

Applicant disagrees that claims 22-24 lack written description in the specification for the reasons set forth above.

With regard to claim 25, the Office Action states that there is inadequate written description about the nucleic acid sequence that "hybridizes" to which "portion" of the complement of the IgG heavy chain constant region of SEQ ID NO:1 and under which "stringent conditions". The Examiner doubts that the sequence will be the whole IgG

heavy chain constant region or the specific Fc domain, let alone encoding a polypeptide that binds to a native IgG inhibitory receptor.

Applicant disagrees. Claim 25 depends from claim 1 and modifies the polypeptide sequence comprising at least 85% identity with an IgG heavy chain constant region such that the polypeptide must also be encoded by a nucleic acid which hybridizes to at least a portion of the complement of SEQ ID NO:1. Accordingly, the claim finds written description throughout the Specification, and is allowable. The Examiner is respectfully requested to withdraw this rejection.

Withdrawal of this rejection is respectfully requested.

4. Rejection under 35 U.S.C. § 112, second paragraph.

Claims 1, 4-5, 9-14, 16-34 and 40-44 stand rejected under 35 U.S.C. 112, second paragraph as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "through a third polypeptide" in claim 1 is indefinite and ambiguous because it is not clear whether the third polypeptide is part of the fusion molecule.

Applicant has amended claim 1 to delete the objected to language rendering this rejection moot. Withdrawal of this rejection is requested.

5. Rejection under 35 U.S.C. § 103(a) over U.S. Patent 5,116,964 in view of U.S. Patent 5,858,980

Claims 1, 4-5, 9-14, 16, 22-28 and 40-41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,116,964 in view of U.S. Patent 5,858,980.

It allegedly would have been obvious to substitute the myelin-associated glycoprotein (MAG) in the IgG heavy chain constant fusion molecule as taught by the '964 patent for the myelin basic protein (MBP) that is 100% identical to at least a portion of the amino acid sequence of myelin basic protein (MBP) as taught by the '980 patent.

Claim 1 recites an isolated fusion molecule comprising a first polypeptide sequence having at least 85% identity with an IgG heavy chain constant region sequence capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of basic myelin protein (MBP) and capable of specific binding to an IgE class immunoglobulin.

The '964 patent allegedly teaches an isolated fusion molecule comprising a first polypeptide such as the constant domain of the IgG heavy chain or the fc portion of human IgG1, IgG2, IgG3, IgG4 fused to a second polypeptide autoantigen sequence such as myelin-associated glycoprotein (MAG) or a portion thereof. The reference MAG is allegedly capable of binding to IgE autoantibodies that are specific for MAG when administered to a human subject, in turn, the MAG specific IgE autoantibodies are allegedly capable of binding to its native IgE receptors. The advantage of the Fc is allegedly to improve the in vivo plasma half-life of the fusion molecule. The '964 patent allegedly teaches a pharmaceutical composition.

The '964 patent does not teach or suggest fusion molecules of the MBP peptide with the IgG heavy chain constant region. The '964 patent does not teach or suggest the administration of an IgG Fc-MBP peptide fusion polypeptide to persons for the treatment of autoimmune disease.

The '980 patent allegedly teaches autoantigen such as human myelin basic protein (MBP) and various fragments of MBP such as SEQ ID NO: 18-23 and 16. The reference MBP peptide of SEQ ID NO:18 is allegedly 100% identical to SEQ ID NO:13.

The '980 patent does not teach or suggest fusion molecules of the MBP peptide with the IgG heavy chain constant region. The '980 patent does not teach or suggest the administration of an IgG Fc-MBP peptide fusion polypeptide to persons for the treatment of autoimmune disease.

In view of the deficiencies in the cited references as described above, the claimed invention is not obvious under 35 U.S.C. § 103 for the following reasons.

As the Examiner is aware there are three requirements to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary

skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999) Moreover, the prior art must suggest the specific modification that is necessary in order to arrive at the claimed invention. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990), cert. denied, 498 U.S. 920 (1990)

Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 ("Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure.").

And third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Here, Applicants submit that the prior art references alone or in combination fail to teach or suggest the claimed invention.

First, there is no teaching in the '964 patent to combine the MAG protein with the Fc region of IgG. The paragraph at column 7, lines 35 – 45 states "As used herein the term "ligand binding partner" specifically *excludes* polymorphic and non-polymorphic members of the immunoglobulin gene super family and proteins which are homologous thereto such as .....myelin associated glycoprotein (MAG)." (emphasis added). MAG is specifically excluded from the described invention.

Second, there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment. While the '980 patent teaches MBP peptides there is no teaching or suggestion to combine the peptide with an IgG Fc region.

Thirdly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '964 patent states that "it is an object of this invention to produce ligand binding partners fused to moieties which serve

to prolong the in vivo plasma half-life of the ligand binding partner, such as immunoglobulin domains or plasma proteins, and facilitate it purification by protein A. It is a further object to provide novel hybrid immunoglobulin molecules which combine the adhesive and targeting characteristics of a ligand binding partner with immunoglobulin effector functions such as complement binding, cell receptor binding and the like. Yet another object is to provide molecules with novel functionalities such as those described above the therapeutic use, or for use as diagnostic reagents for the in vitro assay of the ligand binding partners or their targets. It is another object to provide multifunctional molecules in which a plurality of ligand binding partners (each of which may be the same or different) are assembled, whereby the molecules become capable of binding and/or activating more than one ligand." The '964 patent provides no motivation to replace the LHR peptide with an MBP peptide in which the MBP serves as an immunogen/tolergen. There is no motivation in the '980 patent to attach the MBP peptide to an IgG heavy region. There is no motivation to generate a fusion protein comprising the MBP peptide.

In fact a number of references teach away from the claimed invention. Davidson et al., teaches that two recent phase I clinical trials for treatment of multiple sclerosis by administering altered peptide ligands derived from MBP resulted in either hypersensitivity reactions or exacerbations of multiple sclerosis. Similarly McDevitt indicates that administration of GAD autoantigen epitopes to NOD mice was found to induce immediate hypersensitivity that could lead to death. Accordingly, one would not be motivated to administer MBP to people, much less attach the Fc region to the MBP to increase the half-life of the MBP in the person.

Absent a suggestion in the art to make the claimed invention, a motivation in the cited references to combine the references into the claimed invention and a reasonable expectation of success, the claimed invention is <u>not</u> obvious. Thus, withdrawal of this rejection is respectfully requested.

<u>6. Rejection under 35 U.S.C. § 103(a) over U.S. Patent 5,116, 964 in view of U.S. Patent No. 5,858,980 and further in view of US Patent No. 5,565,335</u>

Claims 18-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,116,964 in view of U.S. Patent No. 5,858,980 and further in view of U.S. Patent 5,565,335. The Office Action states that it would have been obvious to one having ordinary skill in the art at the time to substitute the Fc polypeptide in the fusion protein comprising a first polypeptide at least 85% identity with an IgG heavy chain fused to myelin basic protein as taught by the '964 patent and the '980 patent for the human IgG1 Fc having an amino acid sequence at least 97.2% identical to the calimed SEQ ID NO:3 as taught by the '335 patent. One would allegedly have been motivated because the '335 patent teaches that Fc fusion molecule enhances the plasma half-life of the fusion molecule.

Claim 1 recites an isolated fusion molecule comprising a polypeptide sequence having at least 85% identity with an IgG heavy chain constant region sequence capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of basic myelin protein (MBP) and capable of specific binding to an IgE class immunoglobulin.

U.S. Patent 5,116,964 and US Patent No. 5, 858,980 have been discussed above.

U.S. Patent No. 5,565,335 teaches soluble secreted adhesons comprising the CD4 protein. The CD4 adheson ordinarily binds to the recognition sites of HIV and the purpose of the patent is to design candidates for therapeutically sequestering these HIV sites, thereby blocking viral infectivity. The '335 patent teaches fusing the CD4 polypeptide with a protein with a long plasma life such as an immunoglobulin constant domain. The purpose of this fusion is to increase the half-life of the CD4 polypeptide. The '335 patent teaches the CD4 peptide linked to the IgG1 heavy chain constant region. The '335 patent teaches that adhesons are cell surface polypeptides having an extra-cellular domain which is homologous to a member of the immunoglobulin gene superfamily, excluding however, highly polymorphic members of the superfamily. (Col. 4, lines 7 - 14). The patent lists a number of examples of adhesions. Myelin basic protein is not an adheson. There is no teaching or suggestion of autoantigens. There is no teaching or suggestion in the '335 patent to replace the CD4 molecule in the

immunoadheson with an MBP peptide. Such a replacement would be against the purpose of the '335 patent.

The claimed invention is not obvious under 35 U.S.C. § 103 in light of the references for, at least, the following reasons.

First, there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment.

Secondly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '335 patent teaches CD4 fused with IgG. There is no motivation in the '335 patent to replace the CD4 with an MBP peptide.

Finally, none of the references, either alone or in combination provide a reasonable expectation of success from the claimed invention.

Absent a suggestion in the art to make the claimed invention, a motivation in the cited references to combine the references into the claimed invention and a reasonable expectation of success, the claimed invention is not obvious. Thus, withdrawal of this rejection is respectfully requested.

7. Rejection under 35 U.S.C. § 103(a) over U.S. Patent 5,116,964 in view of U.S. Patent No. 5,858,980 and further in view of Elias et al. and Marks et al.

Claims 29-34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,116,964 in view of U.S. Patent No. 5,858,980 and further in view of Elias et al., (J. Biol. Chem 265(26) 15511-17, (1990) and Marks et al., (J. Cell Biol. 135(2) 341-354, (1996). The Office Action states that it would have been obvious to include at least one amino terminal ubiquitination target motif such as large hydrophobic amino acid residue such as leucine as taught by Elias and Marks to the fusion molecule comprising IgG heavy chain constant region fused to a second autoantigen polypeptide of myelin basic protein as taught by the '964 patent and the '980 patent. From the combined teachings it allegedly would have been apparent that one would have had a reasonable expectation of success in producing the claimed invention.

This rejection is traversed for the following reasons.

The claimed invention is not obvious in light of the combination of the cited references for the following reasons.

The '964 patent and the '980 patent have been discussed above.

Elias et al. teach that the N terminal residue of the protein is one important structural determinant recognized by ubiquitin ligase to conjugated protein to ubiquitin for protein degradation. Elias et al. teach hydrophobic amino acid residues such as leucine or basic amino acid residues such as histidine, arginine and lysine determine the half-life of the protein. Elias does not teach the elements which are missing from the '964 patent or the '980 patent.

Mark et al. teach that adding ubiquitination target motifs such as bulky hydrophobic group di-leucine motifs to any protein would target the protein to the lysosome or endosomal compartments for antigen processing. Mark does not teach the elements which are missing from the '964 patent or the '980 patent.

First, there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment. The '964 patent and the '980 patent do not teach or suggest the fusion of a heavy constant region of the IgG molecule with a myelin basic peptide fragment for ther reasons set forth above. The Elias and Marks references do not cure this deficiency.

Secondly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '964 patent uses the IgG heavy chain region to increase the plasma half-life of the fusion peptide. It provides no motivation to replace the LHR peptide with an MBP peptide. The Elias and Marks references do not cure this deficiency.

Finally, none of the references, either alone or in combination provide a reasonable expectation of success from the claimed invention.

Absent a suggestion in the art to make the claimed invention, a motivation in the cited references to combine the references into the claimed invention and a reasonable expectation of success, the claimed invention is <u>not</u> obvious. Thus, withdrawal of this rejection is respectfully requested.

8. Rejection under 35 U.S.C. § 103(a) over U.S. Patent 5,116,964 in view of U.S. Patent 5,858,980, and further in view of U.S. Patent No. 5,945,294

Claims 42-44 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,116,964 in view of U.S. Patent 5,858,980 and further in view of U.S. Patent No. 5,945,294. The Office Action states that it allegedly would have been obvious to substitute the human Fc epsilon receptor as taught by the '294 patent for the fusion protein as taught by the '964 patent, in the kit for diagnostic assays.

Claim 1 recites an isolated fusion molecule comprising a first polypeptide sequence having at least 85% identity with an IgG heavy chain constant region sequence capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of basic myelin protein (MBP) and capable of specific binding to an IgE class immunoglobulin.

The '964 patent and the '980 patent have been discussed above.

The '294 patent teaches diagnostic kits for IgE detection comprising human Fc epsilon receptor and an allergen.

Neither the '964 patent, the '980 patent nor the '294 patent nor a combination of all three teaches or suggests the fusion protein of the IgG Fc region with the MBP peptide in a kit. Absent such a teaching or suggestion, the invention is not obvious within the meaning of 35 U.S.C. § 103.

Thus, withdrawal of this rejection is respectfully requested.

Applicant notes with appreciation that Claim 17 is free of the prior art.

9. Conclusion

Applicants submit that the present claims are in condition for allowance, and respectfully request issuance of a notice of allowance. If the Examiner believes that any matters remain outstanding, however, applicants respectfully invite the Examiner to call the undersigned to schedule a telephonic interview.

Respectfully submitted,

Date: October 2, 2006

Leslie A. Mooi
Reg. No. 37,047

HELLER EHRMAN LLP
Customer No. 25213
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2235991 v1
10/2/06 4:19 PM (39754.0674)